First-in-Human Study of the CD123 NK Cell Engager SAR443579 in Relapsed or Refractory Acute Myeloid Leukemia, B-Cell Acute Lymphoblastic Leukemia or High-Risk Myelodysplasia: Updated Safety, Efficacy, Pharmacokinetics and Pharmacodynamics

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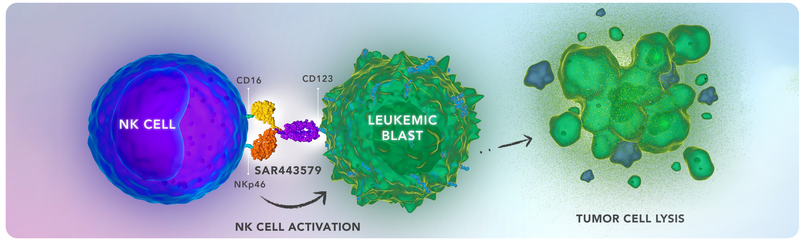
BACKGROUND

- Cluster of differentiation 123 (CD123) is widely expressed in hematological malignancies[1–4]
- T cell engagers targeting CD123 have displayed some preliminary clinical efficacy; however, they have been associated with safety concerns including cytokine release syndrome and neurotoxicity[5]
- SAR443579 (SAR'579) is a trifunctional anti-CD123 NKp46xCD16 natural killer cell engager (NKCE) targeting the CD123 antigen and co-engaging NKp46 and CD16a on natural killer (NK) cells triggering tumor cell death (**Figure 1**)
- TCD17197 (NCT05086315) is an ongoing first-in-human phase 1/2 open-label, multicenter trial evaluating SAR'579 in patients with relapsed or refractory acute myeloid leukemia (R/R AML), B-cell acute lymphoblastic leukemia (B-ALL) or high-risk myelodysplasia (HR-MDS)
- Early clinical results demonstrated that SAR'579 was well tolerated up to 3000 µg/kg/infusion once daily (QW) with no dose-limiting toxicities; clinical remissions were identified at a maximal target dose of 1000 µg/kg/infusion[6,7]
- Here we present updated results from TCD17197 on SAR'579 doses ranging from 10 µg/kg through 6000 µg/kg at a data cutoff of October 23, 2023

Figure 1: Mechanism of Action



CD, cluster of differentiation; NK, natural killer.

METHODS

Study Design

- Patients received SAR'579 intravenously twice weekly or once weekly (QW), depending on dose level (DL), for the first 2 weeks of cycle 1, and QW for rest of the induction cycles (**Figure 2**)
- Patients received approximately three 28-day induction cycles and, upon achieving a complete remission (CR) or incomplete hematologic recovery (CRi) per modified International Working Group criteria,[8] could transition to a 56-day maintenance period with dosing approximately every 29 days if not a candidate for stem cell transplantation
- Peripheral blood (to determine plasma concentrations and immunogenicity) and bone marrow samples were collected for pharmacokinetic/pharmacodynamic (PK/PD) analysis during each induction cycle
- Primary objectives: safety/tolerability and preliminary anti-leukemic activity (composite complete remission [CRc]=CR+CRi)

Figure 2: First-in-Human Dose Escalation and Expansion

Dose Escalation

Determine maximum tolerated or administered dose based on incidence of dose-limiting toxicity in cycle 1 (28-day cycles)

R/R-AML, HR-MDS, B-ALL
8 initial dose levels (Bayesian Logistic Regression Model)

Dose Expansion

Determination of CRc (CR +CRi)

- Cohort A – Primary induction failure & early relapse AML
- Cohort B – Late relapse AML

IV Dose in µg/kg	DL1	DL2	DL3	DL4	DL5	DL6	DL7	DL8
Day 1	10	30	100	300	1000	3000	6000	1000
Day 4	30	100	300	/	/	/	/	/
Day 8	100	300	1000	100	3000	3000	6000	1000
Day 11	100	300	/	/	/	/	/	/
Day 15	100	300	1000	1000	3000	3000	6000	1000
Day 22	100	300	1000	1000	3000	3000	6000	1000

- Additional induction cycles (28 days) were allowed using Day 22 dose (QW)

Key Eligibility Criteria

- Age ≥12 years
- Eastern Cooperative Oncology Group ≤2 (age ≥18 years), Karnofsky ≥50% (age 16–17 years), or Lanksy ≥50% (age <16 years)
- Prior transplant allowed if relapse >3 months and off immunosuppression and no graft-versus-host disease
- Steroids allowed if ≤10 mg/day of oral prednisone or equivalent (inhaler, nasal spray, ophthalmic solution exceptions)
- Confirmed CD123+ for HR-MDS and B-ALL
- No active central nervous system leukemia
- No prior anti-CD123 directed agents
- No tocilizumab within 14 days of investigational medicinal product
- White blood cell count (WBC) <15x10⁹/L

AML, acute myeloid leukemia; B-ALL, B-cell acute lymphoblastic leukemia; CD123, cluster of differentiation 123; CR, complete remission; CRc, composite CR; CRi, CR with incomplete hematological recovery; DL, dose level; HR-MDS, high-risk myelodysplasia; IV, intravenous; QW, once weekly; R/R-AML, relapsed or refractory acute myeloid leukemia.

RESULTS

- A total of 43 patients were included in this analysis; of those, 3 (7%) remain on treatment and 40 (93%) have discontinued treatment (adverse events, n=2; progressive disease, n=31; patient withdrawal, n=3; other, n=4)
- Patients received a median of 2.0 cycles (range: 1–11) of treatment with a median treatment duration of 7.9 weeks (range: 1–65)

Table 1: Baseline Characteristics

Characteristic	N=43
Age, median (range), years	68 (21–81)
18–65, n (%)	19 (44.2)
66–75, n (%)	17 (39.5)
>75, n (%)	7 (16.3)
Female, n (%)	15 (34.9)
ECOG PS, n (%)	
0	8 (18.6)
1	33 (76.7)
2	2 (4.7)
AML diagnosis, n (%)	42 (97.7)
HR-MDS diagnosis, n (%)	1 (2.3)

Characteristic	N=43
WBC at baseline,* median (range), 10⁹/L	2.8 (0–12)
Blast count in blood,* median (range), 10⁹/L	0.8 (0–29)
Blast proportion in bone marrow,† %, median (range)	50.0 (3–90)
Extramedullary disease,* n (%)	7 (16.7)
Prior lines of therapy, median (range)	2.0 (1–10)
1, n (%)	16 (37.2)
2, n (%)	11 (25.6)
≥3, n (%)	16 (37.2)
Prior HSCT, n (%)	13 (30.2)
Prior venetoclax, n (%)	36 (83.7)

*Reported in 42 patients. †Reported in 39 patients.
AML, acute lymphoblastic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; HR-MDS, high-risk myelodysplasia; HSCT, hematopoietic stem cell transplantation; WBC, white blood cells.

Figure 3: Individual Patient Responses per Investigator

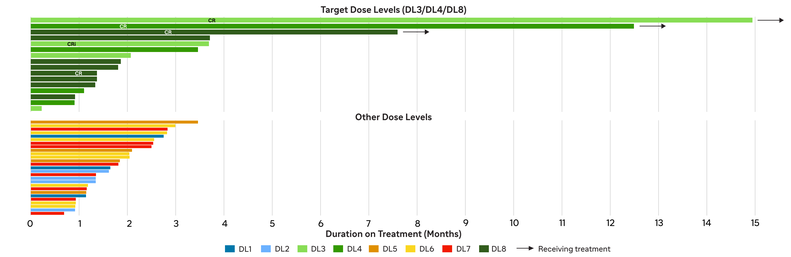


Table 2: Response per Investigator (per Modified IWG criteria[8])

	DL1 (n=3)	DL2 (n=4)	DL3 (n=4)	DL4 (n=4)	DL5 (n=4)	DL6 (n=8)	DL7 (n=8)	DL8 (n=7)	All (N=42)
Maximum target dose (µg/kg)	100	300	1000	1000	3000	3000	6000	1000	–
CRc, n (%)	0	0	2 (50.0)*	1 (25.0)	0	0	0	2 (28.6)	5 (11.9)

*1 CRi
CR, complete remission; CRc, composite CR (CR+CRi); CRi, CR with incomplete hematological recovery; DL, dose level; IWG, International Working Group.

- CR/CRi was reported in 5 of 15 (33.3%) patients with R/R AML treated at a maximal target dose of 1000 µg/kg/infusion; 3 patients with CR are still receiving treatment
- The median duration of response was not estimable; maximum time on treatment was 65 weeks
- 4 responders had prior venetoclax and 2 had prior HSCT

Table 3: Summary of Adverse Events

n (%)	DL1 (n=3)	DL2 (n=4)	DL3 (n=4)	DL4 (n=4)	DL5 (n=4)	DL6 (n=8)	DL7 (n=8)	DL8 (n=8)	All (N=43)
Dose-limiting toxicities	0	0	0	0	0	0	0	0	0
TEAEs (all grades)	3 (100)	4 (100)	4 (100)	4 (100)	4 (100)	7 (87.5)	8 (100.0)	8 (100.0)	42 (97.7)
Grade ≥3	3 (100)	3 (75.0)	3 (75.0)	3 (75.0)	3 (75.0)	5 (62.5)	3 (37.5)	3 (37.5)	26 (60.5)
Grade 5	0	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	0	1 (12.5)	0	5 (11.6)
TRAEs (all grades)	2 (66.7)	4 (100)	2 (50.0)	4 (100)	3 (75.0)	4 (50.0)	6 (75.0)	7 (87.5)	32 (74.4)[†]
Treatment-emergent SAEs	2 (66.7)	3 (75.0)	3 (75.0)	3 (75.0)	3 (75.0)	5 (62.5)	2 (25.0)	3 (37.5)	24 (55.8)
Treatment-related SAEs	0	0	2 (50.0)	0	0	0	0	0	2 (4.7)[†]

[†]Grade ≥3 TRAEs were reported in 2 patients
[‡]Grade ≥3 treatment-related SAEs were reported in 1 patient (diverticulitis)
DL, dose level; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

- No dose-limiting toxicities were reported up to the highest dose of 6000 µg/kg QW
- The most common TEAEs included infusion-related reactions (67.4%) and constipation (25.6%)
- Grade 5 TEAEs included cholestasis, nontraumatic intracranial hemorrhage, lobular pneumonia, lung sepsis, and urosepsis; all grade 5 events were unrelated to SAR'579
- No TEAEs led to the permanent discontinuation of SAR'579

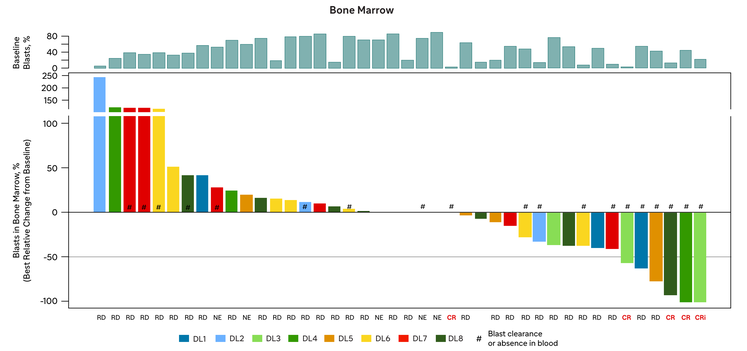
Table 4: TRAEs Reported in ≥4% of all Patients

n (%)	DL1 (n=3)	DL2 (n=4)	DL3 (n=4)	DL4 (n=4)	DL5 (n=4)	DL6 (n=8)	DL7 (n=8)	DL8 (n=8)	All Grade (N=43)	Grade ≥3 (N=43)
Infusion-related reaction	1 (33.3)	3 (75.0)	2 (50.0)	4 (100.0)	2 (50.0)	4 (50.0)	6 (75.0)	7 (87.5)	29 (67.4)	0
Cytokine release syndrome	0	0	0	1 (25.0)*	1 (25.0)*	0	0	0	2 (4.7)*	0
Decreased appetite	0	1 (25.0)	0	0	1 (25.0)	0	0	0	2 (4.7)	0
Diarrhea	1 (33.3)	1 (25.0)	0	0	0	0	0	0	2 (4.7)	0
Nausea	1 (33.3)	0	0	0	1 (25.0)	0	0	0	2 (4.7)	0

*Grade 1. Events are per patient (i.e. an individual may have multiple concurrent AEs).
AE, adverse events; C, cycle; D, day; DL, dose level; TRAE, treatment-related adverse event.

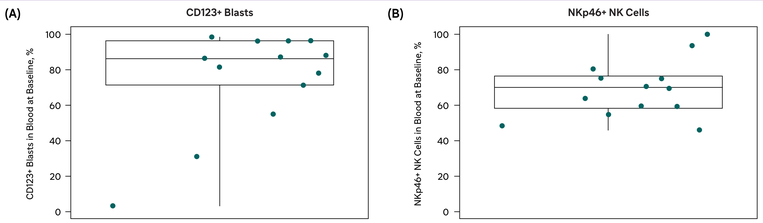
- The most common TRAE was infusion-related reaction, which generally occurred during cycle 1/day 1 and typically resolved within 1 hour utilizing temporary interruption of infusion and symptom management
- Grade ≥3 TRAEs were reported in 2 patients and included grade 3 diverticulitis in 1 patient in DL3 and grade 4 neutropenia in 1 patient in DL3
- There were no cases of immune effector cell-associated neurotoxicity syndrome

Figure 4: AML Blast Assessment



CR, complete remission; CRi, CR with incomplete hematological recovery; NE, non-evaluable; RD, resistant disease.

Figure 5: Expression of (A) CD123 and (B) NKp46 in blood



NK, natural killer.

- High variability was seen in baseline AML blasts (**Figure 4**)
- AML blast reductions were observed across all SAR'579 dose levels (**Figure 4**)
- CD123 expression was observed in all patients (**Figure 5A**)
- Robust expression (>50%) of NKp46 was seen in all patients (**Figure 5B**)

SUMMARY AND CONCLUSIONS

- SAR'579 was well tolerated up to doses of 6000 µg/kg QW with clinical benefit in patients with R/R AML; additional dose levels are being investigated
- CR/CRi was reported in 33.3% of patients with R/R AML treated at a maximal target dose of 1000 µg/kg/infusion, and 3 responders continue on treatment
- The median duration of response was not estimable and is ongoing
- There were no dose-limiting toxicities
- Infusion-related reaction was the most common treatment-related adverse event
- The grade ≥3 TRAEs reported in the study were grade 3 diverticulitis and grade 4 neutropenia (in 1 patient each)
- Cytokine release syndrome (grade 1) was observed in 1 patient at DL4 and 1 at DL5
- There were no reports of immune effector cell-associated neurotoxicity syndrome
- PD data are consistent with those previously reported;[7] CD123 expression was observed in all patients
- SAR'579 continues to be investigated in hematological malignancies and was granted FDA Fast Track designation in May 2023

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REFERENCES:
1. Lyapichev KA, et al. *Clin Lymph Myel Leuk.* 2021;21(4): e317–e320.
2. Patnaik MM, et al. *Leuk Lymphoma.* 2021;62(11):2568–86.
3. Uckun FM, et al. *Front Aging.* 2021;2:757276.
4. El Achi H, et al. *Cancers (Basel).* 2020;12(11):3087.
5. Uy GL, et al. *Blood.* 2021;137(6):751–62.
6. Stein AS, et al. *J Clin Oncol.* 2023;41(suppl 16): 7005.
7. Jongen-Lavrencic M, et al. *Ann Oncol.* 2023;34(Suppl_2):8230.
8. Cheson BD, et al. *J Clin Oncol.* 2003;21(24):4642-9.

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